Journal of Neurological Sciences [Turkish] **28:(3)**# 28; 347-354, 2011
http://www.jns.dergisi.org/text.php3?id=457

Research Article

The Outcome of Surgically Resected Anaplastic Astrocytoma and Glioblastoma: Results of Single Center Retrospective Study

Erdal Reşit YILMAZ, Bora GÜRER, Hayri KERTMEN, Habibullah DOLGUN, Ahmet Metin ŞANLI, Zeki ŞEKERCI

Ministry of Health, Diskapi Yildirim Beyazit Education and Research Hospital, 1st Neurosurgey Clinic, Ankara, Türkiye

Summary

Objective: Anaplastic astrocytomas and glioblastomas are the most common primary cerebral neoplasms in adults. Unfortunately, despite newly developed therapies and surgical techniques, the clinical course of anaplastic astrocytomas and glioblastomas is very rapid and almost always they have miserable prognosis. We report the outcome of surgically resectioned anaplastic astrocytomas and glioblastomas in our clinic.
Methods: We retrospectively analyzed the records including age of diagnosis, preoperative Karnofsky performance score, survival period, histological grade of the tumor; extend of surgical resection, and postoperative treatment status of all anaplastic astrocytomas and glioblastomas operated. The patients (n=164) who died in this period have been included in this study.
Results: Overall survival of the patients with anaplastic astrocytomas was 25.4 months; and 8.3 months for glioblastomas; six months progression free survival was 42.5% for patients with anaplastic astrocytomas; and 14.5% for those with glioblastomas. Six months and 1 year survival rates of gross total removal plus near total removal group were 76.8% and 45.8% respectively. Six months and 1 year survival rates of subtotal removal group was 55.6% and 22.2% respectively.
Conclusion: As expected, overall survival tends to be longer for patients with anaplastic astrocytomas. Overall survival and life expectation were longer for patients with six months progression free survival. Preoperative high Karnofsky performance score and younger age at the time of diagnosis were associated with good prognosis. Gross total removal plus near total removal group had higher survival rates compared with subtotal removal group and biopsy groups.

Key words: Anaplastic astrocytoma, glioblastoma, outcome, surgery, progression free survival

Cerrahi Çıkarım Yapılan Anaplastik Astrositomların ve Glioblastomların Sağkalım Analizi: Tek Merkezli Retrospektif Çalışma Sonuçları

Özet

Amaç: Anaplastik astrositomlar ve glioblastomlar en sık görülen primer santral sinir sistemi neoplazmıdır. Ne yazık ki, gelişen tedavi yöntemlerine ve cerrahi tekniklere rağmen bu tümörlerin klinik seyirleri çok hızlıdır ve prognozları hemen her zaman kötüdür. Bu çalışmada, kliniğimizde cerrahi uygulanan anaplastik astrositomların ve glioblastomların sağ kalım analizi yapılmıştır.

Yöntem: Kliniğimizde Ocak 2005 ile Aralık 2009 tarihleri arasında opere edilen anaplastik astrositom ve glioblastom tanılı hastaların tanı anındaki yaşları, ameliyat öncesi Karnofsky performans skorları, sağ kalım süreleri, tümörün histopatolojik evresi, cerrahi çıkarım oranı ve ameliyat sonrası tedavi durumları geriye dönük olarak analiz edildi. Bu periyotta ölen 164 hasta çalışmaya dahil edildi.

Bulgular: Anaplastik astrositomların ortalama sağ kalım süresi 25.4 ay; glioblastomların ortalama sağ kalım süresi ise 8.3 ay olarak bulundu. 6 aylık progresyonsuz sağ kalım anaplastik astrositomların %42.5'inde; glioblastomların %14.5'inde sağlanmıştır. Gross total ve totale yakın cerrahi çıkarım yapılan hastaların 6 aylık ve 1 yıllık sağ kalım oranları sırasıyla, %76.8 ve %45.8 olarak bulunmuştur; subtotal çıkarım yapılan hastalarda ise bu oranlar %55.6 ve %22.2 olarak bulunmuştur.

Sonuç: Beklendiği üzere anaplastik astrositomların sağ kalım oranları daha uzundur. 6 ay progresyonsuz sağ kalım sağlanan hastaların uzun süreli sağ kalım oranları ve yaşam beklentileri daha fazladır. Ameliyat öncesi yüksek Karnofsky performans skoru olan ve tanı anında daha genç yaşta olan hastaların prognozları daha iyidir. Gross total ve totale yakın çıkarım yapılan hastaların sağ kalım oranları subtotal çıkarım yapılan ve biopsi yapılan gruplardan daha fazladır.

Anahtar Kelimeler: Anaplastik astrositom, glioblastoma sağ kalım, cerrahi, progresyonsuz sağ kalım

INTRODUCTION

High-grade or malignant gliomas belong to World Health Organization (WHO) classification, grade III and IV[7], are the most common primary intracranial neoplasm in adults. Glioblastomas (WHO Grade IV) account for approximately 60% to 70% of high-grade gliomas, anaplastic astrocytomas (WHO Grade III) for 10% and anaplastic oligoastrocytoma (WHO Grade III) for 10%[7,11]. High-grade gliomas are more common in men, and the median age of diagnosis is 64 years in the case of glioblastoma, and 45 years in the case of anaplastic astrocytoma[7,11]. No underlying cause has been identified for the majority of high-grade gliomas. The only established risk factor is exposure to ionizing radiation[4]. Approximately %5 of patients with high grade gliomas has a family history of gliomas[3].

Unfortunately, despite newly developed therapies and surgical techniques, the clinical course of high-grade gliomas is very rapid and almost always they have miserable prognosis[11]. Median survival for patients with glioblastoma is in the range of 9-12 months; and 2 to 4 years for patients with anaplastic astrocytomas[1,5,8,11].

In this retrospective study, we report the results of outcome of the surgically resected anaplastic astrocytomas and glioblastomas of our neurosurgery clinic.

MATERIAL AND METHODS

We retrospectively analyzed all anaplastic astrocytomas and glioblastomas operated during January 2005 to December 2009 at

the 1st Neurosurgery Clinic, Diskapi Yildirim Beyazit Education and Research Hospital. The patients (n=164) who died in this period included to this study; and patients who are still on follow-up were excluded from the study.

Records included age of diagnosis, preoperative Karnofsky performance score (KPS), survival period, histological grade of the tumor, extend of surgical resection, and postoperative treatment status in all patients. WHO grade III oligodendrogliomas, oligoastrocytomas and ependymomas were excluded from this study. Postoperative magnetic resonance imaging (MRI) with contrast was obtained at the sixth postoperative month in all patients who performed to survive till this time (n=122, 74.3%). Follow-up was possible for all patients. Of all patients who survived from surgery (n=154, 93.9%) underwent radiotherapy and most (n=96, 58.5%) received chemotherapy with temozolamide (TMZ).

The extent of surgical resection was qualitatively determined by the operating surgeon, combining intraoperative observations with interpretation of postoperative contrast enhanced computerized tomography or MRI. Resection was defined as gross total and near total resection (>90% resection), subtotal resection (10-90%) or biopsy (<10%).

Six months progression free survival (6moPFS) is evaluated with MRI, neurological findings of the patients and the steroid dose at that time. Objective response for measurable disease required a decrease in tumor size of %50 or greater in the setting of stable neurological findings and no increase in steroid dose.

Statistical Analysis

Categorical variables are expressed as percentages. Survivals were estimated by using the Kaplan–Meier method and curves were compared by using the log-rank test. Survival time was calculated from the date of diagnosis until death. The effect of potential risk factors on the overall survival were evaluated with Cox proportional hazards models. The threshold for statistical significance was $P<0.05$. Analyses were performed with SPSS for Windows version 11.5 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

The demographic data are summarized in Table-1. Mean age was 51.8 years (±16.4 yr) and the age range was from 9 to 86 years. The population of the study was comprised of 164 patients (54 with anaplastic astrocytoma, and 110 with glioblastoma). Overall survival of the patients with anaplastic astrocytoma was 25.4 months (range, 9-55); and 8.3 months (range, 0-31) for glioblastomas. As expected, overall survival tend to be longer for patients with anaplastic astrocytoma ($p<0.001$). 6moPFS was 42.5% for patients with anaplastic astrocytoma and 14.5% for those with glioblastomas. The 6-, 12- and 36-month survival rates were 100%, 92%, 14.8% respectively for patients with anaplastic astrocytoma; and 59%, 17%, 0% for those with glioblastoma. 119 patients were survived longer than 6 months, and 6moPFS was 32.7% (n=39). Overall survival and life expectation were longer for patients with 6moPFS ($p<0.001$).

Preoperative high KPS ($p<0.001$) and younger age at the time of diagnosis ($p=0,044$) were associated with good prognosis.

The prognosis by surgical respectability was also analyzed. Operative mortality was 6.2% (n=10). Gross total removal (GTR) and near total removal (NTR) were achieved in 142 patients (86.5%), subtotal removal (STR) in 18 patients (10.9%), and biopsy was conducted in 4 patients (2.6%). The mean survival of GTR+NTR group was 15 months, and mean survival of STR and biopsy groups were 8 months and 2.8 months respectively. Six months and 1 year survival rates of GTR+NTR group was 76.8% and 45.8% respectively. Six

months and 1 year survival rates of STR group was 55.6% and 22.2% respectively. No patient in biopsy group achieved to live longer than 3 months. GTR+NTR group had higher survival rates compared with STR and biopsy groups ($p<0.001$).

Survival rates and life expectations were summarized in Table-2. Risk factors that were effecting overall survival were summarized in Table-3.

Table 1. Patient characteristics

Parameter	**Value**
Age (y)	
Mean	51.8
Range	9-86
Gender	
Male	106 (64.6)
Female	58 (35.4)
Tumour Grade	
Anaplastic Astrocytoma	54 (32.9)
Glioblastoma	110 (67.1)
Resection	
Biopsy only	4 (2.4)
Subtotal	18 (11.0)
Gross total + Near Total	142 (86.6)

Table 2. Factors effecting life expectation and survival rates

Factor	N	Survival Rates (%)			Median Life Expectation (95% CI)	Log Rank	p
		6-mo	1-yr	3-yr			
Sex						1.35	0.246
Male	106	71.7	40.6	6.6	11 (10-12)		
Female	58	74.1	44.8	1.7	11 (9-13)		
Grade						96.48	<0.001
Anaplastic Astrocytoma	54	100.0	92.6	14.8	22 (19-25)		
Glioblastoma	110	59.1	17.3	0.0	8 (7-9)		
Surgery						33.29	<0.001
BX	4	0.0	-	-	3 (2-4)		
GT	142	76.8	45.8	5.6	11 (9-13)		
ST	18	55.6	22.2	-	7 (3-11)		
Intraoperative Complication						161.09	<0.001
None	154	77.3	44.8	5.2	11 (10-12)		
Present	10	-	-	-	0 (0-1)		
Postoperative Adjuvant Treatment						190.41	<0.001
None	20	-	-	-	2 (1-3)		
Received	144	82.6	47.9	5.6	12 (10-14)		
6moPFS						28.33	<0.001
No	80	100.0	45.0	1.2	11 (10-12)		
Yes	39	100.0	84.6	17.9	23 (19-27)		
TOTAL	164	72.6	42.1	4.9	11 (10-12)	-	-

CI: Confidence Interval
BX: Biopsy. GT: Gross total resection. ST: Subtotal resection 6moPFS: 6 month progression free survival

Table 3. Relative risk ratios effecting overall survival

Independent Variable	Relative Risk	p value	95% Confidence Interval
Glioblastoma	6.053	<0.001	3.961-9.250
Pre-op Karnofsky Score	0.943	<0.001	0.927-0.960
Postoperative Treatment	0.118	<0.001	0.042-0.329
BX	7.385	0.003	2.012-27.104
ST	1.692	0.059	0.981-2.918
Age	1.010	0.044	1.000-1.020
Female gender	1.199	0.301	0.850-1.691
Peroperative Complication	0.741	0.616	0.229-2.394

BX: Biopsy. ST: Subtotal resection.

DISCUSSION

High-grade gliomas are histologically heterogeneous and invasive tumors that are derived from glia. The WHO classifies astrocytomas on the basis of histological features into four prognostic grades: grade I (pilocytic astrocytoma), grade II (diffuse astrocytoma), grade III (anaplastic astrocytoma) and grade IV (glioblastoma). Grade III and IV tumors are considered high-grade or malignant gliomas. Anaplastic astrocytomas are characterized by increased cellularity, nuclear atypia, and mitotic activity. Glioblastomas also contain areas of microvascular proliferation, necrosis or both[6]. Grade III oligodendrogliomas, oligoastrocytomas and ependymomas are also rare types of high grade gliomas. In order to avoid confusion, we excluded these tumors from this study because of their different behavior and prognosis from pure astrocytomas.

High grade gliomas are the most common and poorly prognosed primary cerebral neoplasm in adults. There are several presumed reasons for poor prognosis. First, the tumor cells in the high-grade gliomas extensively infiltrate the surrounding brain parenchyma, thereby limits the overall utility of surgical resection. Second, blood-brain barrier is an obstacle to the adequate delay of chemotherapeutic agents to brain tumors. Third, high-grade gliomas are refractory to most cancer cytotoxic agents and the occasional responses are often short lived with the rapid development of resistance[9]. Therefore, surgical resection alone has limitations in the treatment of high-grade gliomas.

The standard therapy for high-grade gliomas consists of surgical removal to the extent that is safely feasible, followed by radiotherapy with or without adjuvant chemotherapy[11]. Stupp et al.[10], reported that the concomitant administration of

TMZ with fractionated radiotherapy followed by six cycles of adjuvant TMZ for newly diagnosed glioblastoma resulted in a clinically meaningful and statistically significant survival benefit. Patients with malignant gliomas may present variety of symptoms, including headaches, seizures, focal neurologic deficits, confusion, memory loss and personality changes. The diagnosis of high-grade gliomas is usually suggested by MRI or computed tomography. These imaging studies typically show a heterogeneously enhancing mass with surrounding edema. Glioblastomas frequently have central areas of necrosis and more extensive peritumoral edema than that associated with anaplastic glioma. Proton magnetic resonance detects the level of metabolites and may help differentiate a tumor from necrosis or benign lesions[11].

As our study also introduced, the most important adverse prognostic factors in patients with anaplastic astrocytomas and glioblastomas are advanced age, histological features of glioblastoma, poor KPS and unresectable tumor[2]. The North American Brain Tumor Consortium currently uses 6moPFS as prognostic criteria[6]. Objective radiologic response, usually determined by area or volume changes in contrast enhancement on MRI. Because of the aggressive nature of these tumors, 6moPFS was also thought to be a clinical meaningful goal.

Correspondence to:

Bora Gürer
E-mail: boragurer@gmail.com

Received by: 09 July 2011
Revised by: 18 August 2011
Accepted: 19 August 2011

The Online Journal of Neurological Sciences (Turkish) 1984-2011
This e-journal is run by Ege University Faculty of Medicine,
Dept. of Neurological Surgery, Bornova, Izmir-35100TR
as part of the Ege Neurological Surgery World Wide Web service.
Comments and feedback:
E-mail: editor@jns.dergisi.org
URL: http://www.jns.dergisi.org
Journal of Neurological Sciences (Turkish)
Abbr: J. Neurol. Sci.[Turk]
ISSNe 1302-1664

REFERENCES

1. *Choi JW, Lee MM, Kim IA, Kim JH, Choe G, Kim CY. The outcomes of concomitant chemoradiotherapy followed by adjuvant chemotherapy with temozolomide for newly diagnosed high grade gliomas: the preliminary results of single center prospective study. J Korean Neurosurg Soc 2008; 44: 222-7*
2. *Curran WJ Jr, Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, Chang CH, Rotman M, Asbell SO, Krisch RE, et al. Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. J Natl Cancer Inst 1993; 85: 704-10*
3. *Farrell CJ, Plotkin SR. Genetic causes of brain tumors: neurofibromatosis, tuberous sclerosis, von Hippel-Lindau, and other syndromes. Neurol Clin 2007; 25: 925-46*
4. *Fisher JL, Schwartzbaum JA, Wrensch M, Wiemels JL. Epidemiology of brain tumors. Neurol Clin 2007; 25: 867-90*
5. *Galanis E, Buckner JC. Chemotherapy of brain tumors. Curr Opin Neurol 2000; 13: 619-25*
6. *Lamborn KR, Yung WK, Chang SM, Wen PY, Cloughesy TF, DeAngelis LM, Robins HI, Lieberman FS, Fine HA, Fink KL, Junck L, Abrey L, Gilbert MR, Mehta M, Kuhn JG, Aldape KD, Hibberts J, Peterson PM, Prados MD; North American Brain Tumor Consortium. Progression-free survival: an important end point in evaluating therapy for recurrent high-grade gliomas. Neuro Oncol 2008; 10: 162-70*
7. *Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P. The 2007 WHO classification of tumors of the central nervous system. Acta Neuropathol 2007; 114: 97-109*
8. *Mahaley MS Jr, Mettlin C, Natarajan N, Laws ER Jr, Peace BB. National survey of patterns of care for brain-tumor patients. J Neurosurg 1989; 71: 826-36*

9. *Stupp R, Hegi ME, Gilbert MR, Chakravarti A. Chemoradiotherapy in malignant glioma: standard of care and future directions. J Clin Oncol 2007; 25: 4127-36*
10. *Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005; 352: 987-96*
11. *Wen PY, Kesari S. Malignant gliomas in adults. N Engl J Med 2008; 359: 492-507*